

Randomized, Placebo-Controlled Trial of HA-1A, a Human Monoclonal Antibody to Endotoxin, in Children with Meningococcal Septic Shock

Bert Derkx, Janet Wittes, Richard McCloskey, and the European Pediatric Meningococcal Septic Shock Trial Study Group*

From the Academic Medical Center, University of Amsterdam, Emma Children's Hospital AMC, Department of Pediatrics, Amsterdam, the Netherlands; Statistics Collaborative, Inc., Washington, D.C., USA; and Centocor, Inc., Malvern, Pennsylvania, USA

Meningococcal septic shock has a rapid onset and characteristic skin hemorrhages that allow bedside diagnosis. Initial plasma endotoxin levels are high and correlate closely with clinical outcome. In a double-blind, randomized, placebo-controlled trial (planned, $n = 270$; actual, $n = 269$), we compared the effectiveness of HA-1A (6 mg/kg of body weight iv; maximum, 100 mg), a human monoclonal antibody to endotoxin, and placebo in reducing the 28-day all-cause mortality rate among children with a presumptive clinical diagnosis of meningococcal septic shock. Treatment groups were well balanced for baseline characteristics and prespecified prognostic variables. In this trial no significant benefit of HA-1A could be demonstrated. The 28-day mortality rates in the intention-to-treat analysis were as follows: placebo, 28%; HA-1A, 18%; reduction in mortality, 33% ($P = .11$, per Fisher's exact test, two-tailed; odds ratio = 0.59; 95% confidence interval for the difference, 0.31–1.05). All patients tolerated HA-1A well, and no antibodies to HA-1A were detected.

Fulminant meningococcal septic shock (MSS) remains a highly fatal disease despite the continuing advances in supportive care [1]. Endotoxin, the lipopolysaccharide (LPS) component of the gram-negative bacterial cell wall, is considered to be the most important bacterial factor in the pathogenesis of systemic meningococcal infections. In patients with *Neisseria meningitidis* bacteremia, initial plasma endotoxin levels correlate closely with morbidity and mortality, and these levels are often several logs higher than commonly observed in other forms of gram-negative septicemia [2–4]. The endotoxin levels are, furthermore, quantitatively associated with key mediators contributing to the host's inflammatory response [4, 5]. The toxic moiety of endotoxin is lipid A, which is relatively well conserved among different gram-negative bacteria [6, 7].

The assumed central role of endotoxin in gram-negative sepsis has led to the investigation of different antibodies directed against the lipid A moiety of endotoxin in several clinical trials. Increased survival has been demonstrated among gram-negative bacteremic patients with septic shock treated with sera obtained from individuals immunized with injections of an *Escherichia coli* mutant (J5) [8]; however, a study of children with severe infectious purpura (mainly due to meningococ-

cemia) found that antiserum to J5 did not significantly alter the clinical course or mortality [9].

Several randomized clinical trials have been performed to study the efficacy of two monoclonal antibodies: E5, a murine IgM, and HA-1A, a human IgM. In the first E5 trial, antibody treatment appeared to augment the survival rate among patients with gram-negative sepsis who were not in shock [10]. This finding was not confirmed in a second study, although a trend toward improved survival rates among treated patients with major organ failure was observed [11]. In both trials the subgroup effects were not shown to differ in magnitude from the effect in the remainder of the patients in the trial.

Two large clinical trials with HA-1A have been published. The first study showed no overall benefit of HA-1A, but significant improvement in the survival rate was observed in a subgroup of patients with gram-negative bacteremia and shock [12]. Again, the effect in this subgroup did not differ significantly from the effect in the other subgroups. A second trial that also showed no overall clinical benefit of HA-1A was discontinued at the first interim analysis because of a nonsignificant survival disadvantage among patients without gram-negative bacteremia [13]. Although these results do not provide clear evidence of increased survival among patients with sepsis, they do not preclude the possibility that anti-endotoxin therapy might be beneficial for certain patients with gram-negative septicemia. The heterogeneity of etiologic organisms and patients with presumed sepsis and time of administration of the study drug may help to explain these disappointing results.

MSS is an ideal model for the study of immunotherapy in sepsis because its rapid onset and characteristic skin hemorrhages allow bedside diagnosis. The aims of this study were to evaluate the efficacy of a single dose of HA-1A in children with MSS and in patient subgroups defined by *N. meningitidis* culture and antigen status. The secondary objective was to assess the safety of HA-1A.

Received 19 May 1998; revised 22 October 1998.

Dr. McCloskey is a full-time employee of Centocor, Inc. Dr. Wittes had a contract from Centocor, Inc., for the analytic plan and performance of the final analysis.

Grant support: Centocor, Inc.

* The institutions and investigators participating in the study are listed in the Appendix.

Reprints or correspondence: H. H. F. Derkx, Academic Medical Center, University of Amsterdam, Emma Children's Hospital AMC, Department of Pediatrics, P.O. Box 22700, 1100 DE Amsterdam, the Netherlands (h.h.derkx@amc.uva.nl).

Clinical Infectious Diseases 1999;28:770–7

© 1999 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/99/2804-0016\$03.00